10-21-04

AF/1615

Express Mail Label No. **EV 336 041 019 US**

Attorney Docket No. 55325-8169.US00

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Lasic *et al.*	EXAMINER: Kishore
APPLICATION NO.: 09/771,151	ART UNIT: 1615
FILED: JANUARY 26, 2001	CONFIRMATION NO: 9729
FOR: **LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION**	

APPELLANT'S BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Appeal Brief - Patents

Sir:

This is an appeal to the Board of Appeals and Interferences from the decision of Examiner Kishore mailed March 1, 2004 in which pending claims 1, 3-9, and 16 stand in final rejection.

The present paper is Appellants' Appeal Brief submitted in compliance with 37 C.F.R. §1.192.

REAL PARTY IN INTEREST

The real party in interest is Alza Corporation, a subsidiary of Johnson & Johnson.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of other appeals or interferences which would directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF THE CLAIMS

The application was initially filed with 18 claims. Claims 2 and 10 were canceled by Amendment filed September 30, 2002. Claims 10-15 and 17-18 were cancelled by Amendment filed June 17, 2003. The final rejection of pending claims 1, 3-9, and 16, as presented in Appendix A, is appealed.

STATUS OF AMENDMENTS

No amendment subsequent to the Final Office action was submitted. Appellants' response dated June 17, 2004 and submitted after final rejection was entered and made of record.

SUMMARY OF INVENTION

The present invention describes a method for preparing liposomes having an entrapped compound in the form of a supersaturated solution (page 3, lines 9-11). The method comprises (i) selecting a compound having a room temperature water solubility capable of at least a two-fold increase when an aqueous solution of the compound is treated (page 3, lines 11-13) by a condition selected from the group consisting of (a) increasing temperature, (b) adding a co-solvent, and (c) changing pH (page 3, lines 16-19); (ii) preparing liposomes at selected size intervals from a supersaturated solution of the compound (page 3, lines 21-23); (iii) analyzing the liposomes for the presence (or absence) of precipitated compound (page 3, lines 23-26); and (iv) selecting liposomes of a size that has no entrapped precipitated compound (page 3, lines 13-14).

ISSUES

The issues on appeal are:

1. Whether claims 1, 3-6, 8-9, and 16 are anticipated under 35 U.S.C. §102(b) by Yamamoto *et al.* (EP Patent Application No. 0 551 169 A1; hereinafter "Yamamoto *et al.*").

2. Whether claims 1, 3-9, and 16 are anticipated under 35 U.S.C. §102(b) by Abra *et al.* (PCT Publication No. WO 98/07409; hereinafter "Abra *et al.*").

3. Whether claim 7 is obvious under 35 U.S.C. §103(a) over Yamamoto *et al.* in combination with Woodle *et al.* (U.S. Patent No. 5,013,556, hereinafter "Woodle *et al.*").

GROUPING OF CLAIMS

With regard to all issues in this Appeal, claims 1, 3-9, and 16 stand or fall together. Claims 1, 3-9, and 16 are presented in Appendix A.

ARGUMENTS

1.0 The Cited Documents

YAMAMOTO ET AL. describe preparation of a liposome composition by the following method:

(i) preparing an aqueous drug solution of a water-soluble drug by warming the aqueous solvent to yield a solution with the drug in saturated concentration or higher (Col. 2, line 57 to Col. 3, line 7; Col. 4, lines 9-11);

(ii) forming liposomes while maintaining the solution at the warmed temperature (Col. 3, lines 7-11; Col. 4, lines 25-34); and

(iii) removing un-encapsulated drug, typically by cooling the solution to "ordinary" temperature (taken to mean 15-25°C -see Col. 3, lines 13-15)(Col. 3, lines 11-13; Col. 4, lines 19-21).

ABRA ET AL. relate to a liposomal composition containing an entrapped cisplatin compound (page 1, lines 6-7). To prepare the liposomes, an aqueous cisplatin solution is heated to a temperature sufficient to achieve a two-fold increase in cisplatin solubility over its room temperature solubility (page 3, lines 12-14). The drug is entrapped in the inner aqueous compartment in dissolved or precipitated form (page 4, lines 34-35).

WOODLE ET AL. describe a liposome composition which contains between 1-20 mole percent of an amphipathic lipid derivatized with a polyalkylether (Col. 4, lines 44-47, such as polyethyleneglycol (Col. 4, lines 47-49).

2.0 Regarding Novelty rejection over Yamamoto *et al.*

According to the MPEP § 2131: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference".

Claims 1 and 16 of the present invention are directed to a method of preparing a liposome composition. The method includes, *inter alia,* the steps of **(ii)** preparing from a supersaturated solution of the compound liposomes at selected size intervals; **(iii)** analyzing the liposomes for the presence of absence of precipitated compound; and **(iv)** based on the analyzing, selecting liposomes of a size that corresponds to liposomes having no entrapped precipitated compound.

Yamamoto *et al.* fail to teach any of steps (ii), (iii), and (iv) as set forth in claims 1 and 16. As noted above, the method of Yamamoto *et al.* is comprised of three steps, namely, (a) preparing a concentrated drug solution (Col. 4, lines 9-11 and 25-30), (b) forming liposomes with the concentrated solution (Col. 4, lines 11-15); and (c) recovering the un-encapsulated drug (Col. 4, lines 16-19). Nowhere do Yamamoto *et al.* teach the steps of "preparing liposomes at selected size intervals" (claimed step (ii)), "analyzing the liposomes as a function of size for the presence of precipitated compound" (claimed step (iii)), or "based on the analyzing selecting a liposome size that corresponds to liposomes having no precipitated compound" (claimed step (iv)).

The Examiner takes the position that Yamamoto *et al.* teach selection of the liposome size to maintain the compound in the form of a supersaturated solution as the abstract states that "the supersaturated solution is at the [sic] room temperature". The Examiner goes on to state that "[t]his implies that the compound is not in a precipitated state and this in turn means that the liposomes in the reference have selected liposomal sizes" (Final Office action, paragraph bridging pages 2-3).

However, anticipation under 35 U.S.C. § 102(b) requires the disclosure of each and every element of a claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 44 USPQ2d 1429, (Fed. Cir. 1997).

As noted above, it is clear that there is no explicit disclosure in Yamamoto *et al.* of the claimed steps involving "preparing liposomes at selected size intervals" (claimed step (ii)), "analyzing the liposomes as a function of size for the presence of precipitated compound" (claimed step (iii)), and "based on the analyzing selecting a liposome size that corresponds to liposomes having no precipitated compound" (claimed step (iv)).

Thus, it would appear that the Examiner is of the mind that Yamamoto *et al.* *implicitly* discloses the claim steps (ii), (iii), and (iv). The Examiner's statement in the Final Office action that the process in Yamamoto *et al.* "implies the compound is not in a precipitated state and *this in turn* means that the liposomes in the reference have selected liposomal sizes" (Final Office action mailed March 17, 2004, paragraph bridging pages 2 and 3). Thus, the Examiner seems to imply that Yamamoto *et al.* *inherently* includes the missing claim steps.

The legal standard with respect to inherent anticipation is that "inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may result* from a given set of circumstances is insufficient to prove anticipation." *Contenental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991). *In re Oelrich,* 666 F.2d 578, 212 USPQ 323 (CCPA 1981).

This legal standard requires that the disclosure of the claim steps (ii), (iii), and (iv) which are missing from the explicit disclosure of Yamamoto *et al.*, be necessarily present in Yamamoto *et al.* This legal standard is well illustrated in the case law, and the Board is urged to consider both *Electro Medical Systems v. Cooper Life Science, Inc.* (34 F.3d 1048 (Fed. Cir. 1994) and *Mehl/Biophile International Cor. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999).

In *Electro Medical Systems v. Cooper Life Science, Inc.*, in a challenge to validity, the court found that the feature not expressly disclosed in the cited patent to Rumelin was not *necessarily* present in the Rumelin patent. The court noted that the

Rumelin patent did not disclose a substantially unpressurized flow of liquid or a continuous liquid curtain even though the reference did disclose a blasting and spraying gun utilizing pressurized liquid, and thus was insufficient to prove anticipation. The court rejected the argument that the device "could be set to any water pressure" as the defendant did not prove that the unpressurized flow is necessarily present in the Rumelin disclosure, and that it would be so recognized by persons of ordinary skill.

In *Mehl/Biophile International Cor. v. Milgraum*, the court found that the claimed feature of "aligning a laser light applicator substantially vertically over a hair follicle opening" was not expressly disclosed in either of the two cited references, a manual for the laser, the RD-1200 Manual, and an article disclosing targeting melanosomes of guinea pig skin with a laser, the Polla article. The challenger Milgraum relied on these two references in a motion for summary judgment of invalidity with different outcomes.

Regarding the RD-1200 manual, the court found that claimed feature was not *necessarily* present, and thus was insufficient to prove anticipation. The manual used the laser for removing tattoos and "an operator...could use the laser according the manual without necessarily aligning the laser substantially vertically over a hair follicle opening" as the "record shows no necessary relationship between the location of a tattoo and the location of hair follicles." The court further found that "[t]he possibility of such an alignment does not legally suffice to show anticipation."

In contrast, the Polla article described holding the laser in contact with the skin and that "pigmented structures in the deep dermis such as hair follicles are affected." Based on this teaching, the court found that the natural result flowing from holding the laser against the skin and targeting the melanosomes contained within the follicular epithelium would necessarily result in the laser being aligned "substantially vertically over a hair follicle opening" as claimed.

The facts in the present situation differ from those relating to the Polla article as the results obtained by Yamamoto *et al.* are not necessarily the results mandated by the present claims. Yamamoto *et al.* teach the drug "is present in the supersaturated state or in the form of solids or crystals." The teaching in Yamamoto *et al.* that the drug

may be present in the form of solids or crystals indicates that the drug is not always present in the supersaturated state as presently claimed. Thus, the steps relating to sizing the liposomes corresponding to a liposome size having no precipitated compound as in the present invention cannot "naturally flow" or be found to be *necessarily* present, since solid or crystals may be present in the composition of Yamamoto *et al.*

Yamamoto *et al.* teach a process of preparing liposomes where the drug "is present in the supersaturated state or in the form of solids or crystals" (Col. 2, lines 21-23). Because the method of Yamamoto *et* al. *could* be used to prepare liposomes with the drug in solid or crystalline form, it cannot be said that Yamamoto *et al.* inherently anticipates the claimed process of preparing liposomes with the drug in supersaturated form, or that the claim steps (ii), (iii), and (iv) that are undisclosed by Yamamoto *et al.* are inherent in the document's disclosure. Consistent with the findings, in the above exemplary cases, the mere possibility of obtaining liposomes with the drug in supersaturated state is insufficient to anticipate the claimed method.

The Examiner further argues that since Yamamoto *et al.* teach that "the drug is in EITHER supersaturated state or in the form of crystals..." (Final Office action, page 3, first full paragraph), Yamamoto *et al.* must have analyzed the liposomes to see whether there was any precipitation in the liposomes. The Examiner goes on to assert that "since the liposomes containing the supersaturated solutions were analyzed and found to contain no precipitate, the selection of the liposomes is implicit" (Final Office action, page 3, first full paragraph).

The above case law with respect to inherent anticipation applies equally to this argument. The court has consistently found that occasional results are not inherent, for purposes of determining whether a patent is anticipated by prior art alleged to inherently include claimed limitations. Because the liposomes of Yamamoto *et al.* can have the drug in the form of crystals, and there is no teaching or guidance for selection of liposomes only with the drug in supersaturated form, the mere possibility that the disclosure of Yamamoto *et al.* might be understood by one of skill in the art to include liposomes in supersaturated condition is insufficient to show that the claimed method

steps (ii), (iii), and (iv) are inherently disclosed therein. One of skill in the art would not necessarily recognize that method steps (ii), (iii), and (iv) are disclosed in Yamamoto *et al.* because Yamamoto *et al.* also teach formation of liposomes containing drug in crystalline form. Thus, the teaching in Yamamoto *et al.* cannot inherently anticipate the claimed method.

Accordingly, because the cited Yamamoto *et al.* reference fails to teach all of the essential elements of the present invention, Appellants urge the Board to overturn the rejection of claims 1, 3-6, 8-9, and 16 based on Yamomoto *et al.*

3.0 Regarding Novelty rejection over Abra *et al.*

Abra *et al.* fail to teach selection of liposome size in order to maintain the compound in the form of a supersatured solution. Specifically, Abra *et al.* fail to teach each of steps (ii), (iii), and (iv) as set forth in independent claims 1 and 16. The method described by Abra *et al.* is comprised of the following steps: (a) heating an aqueous solution of a cisplatin compound to increase the drug's solubility over the room temperature solubility (page 3, lines 5-6), and (b) forming liposomes with the concentrated solution (page 3, lines 6-11). The liposomes may be sized between about 80-120 nm (page 9, lines 14-16). The un-encapsulated drug may further be removed (page 22, lines 20-23). It is to be noted that the liposomal composition of Abra *et al.* contains an entrapped cisplatin compound in "dissolved or precipitated form" (page 4, lines 34-35). Nowhere does Abra *et al.* teach steps of "preparing liposomes at selected size intervals", "analyzing the liposomes as a function of size for the presence of precipitated compound", or "based on the analyzing selecting a liposome size that corresponds to liposomes having no precipitated compound" as presently claimed.

Similar to the rejection over Yamamoto *et al.*, the Examiner is of the mind that Abra *et al.* teach selection of the liposome size to maintain the compound in the form of a supersaturated solution as "the reference teaches entrapment of the active agent EITHER in the dissolved or precipitated state" (Final Office action, page 4, lines 2-4).

As above, the Examiner must be suggesting that Abra *et al.* inherently discloses claim steps (ii), (iii), and (iv). This reasoning fails for all the reasons given above with reference to Yamamoto *et al.* Briefly, inherent anticipation may not be established by probabilities or possibilities, the disclosure must be necessarily present in the reference.

As taught in Abra *et al.*, the entrapped cisplatin is entrapped in "dissolved or precipitated form" (page 4, lines 34-35). Because the liposomes of Abra *et* al. *could* include the cisplatin drug in precipitated form, it cannot be said that Abra *et al.* inherently anticipates the claimed process of preparing liposomes with the drug solely in supersaturated form, or that the claim steps (ii), (iii), and (iv) that are undisclosed by Abra *et al.* are inherent in the document's disclosure. As above, the mere possibility of obtaining liposomes with the drug in supersaturated state is insufficient to anticipate the claimed method.

Because the cited Abra *et al.* reference does not teach all of the essential elements of the present invention, Appellants urge the Board to overturn the rejection of claims 1, 3-9, and 16 based on this reference.

4.0 Regarding the Combination of Yamamoto *et al.* and Woodle *et al.*

According to the MPEP §2142, one of the three requirements to establish a case of *prima facie* obviousness, is that the prior art references teach or suggest all the limitations of the claim.

Claim 1, from which claim 7 indirectly depends, includes the steps of (ii) preparing from a supersaturated solution of the compound liposomes at selected size intervals; (iii) analyzing said liposomes for the presence of absence of precipitated compound; and (iv) based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no precipitated compound. As discussed above, Yamamoto *et al.* fail to show or suggest any one of steps (ii), (iii), or (iv).

The Woodle *et al.* reference is cited merely for the inclusion of lipids derivatized with a hydrophilic polymer (Final Office action, page 4, lines 19-22). Woodle *et al.* make no mention of entrapping a compound in a supersaturated solution form, without

precipitation, due to selection of a liposome size effective to inhibit precipitation of the compound from the supersaturated solution.

Because the combination of the cited Yamamoto *et al.* and Woodle *et al.* references fail to show or suggest each of steps (ii), (iii), and (iv), Appellants urge the Board to overturn the rejection of claim 7 based on a combination of these documents.

CONCLUSIONS

In view of the foregoing remarks, Appellants submit that the pending claims are in condition for allowance and patentably define over the prior art, and urge the Board to overturn the Examiner's rejections.

Respectfully submitted,

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Date: Oct. 19, 2004

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APPENDIX A: CLAIMS ON APPEAL

1. A method for preparing liposomes having an entrapped compound in the form of a supersaturated solution, comprising:

selecting a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH;

preparing from a supersaturated solution of the compound liposomes at selected size intervals;

analyzing said liposomes for the presence or absence of precipitated compound; and

based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no entrapped precipitated compound.

3. The method of claim 1, wherein selecting the liposomes comprises selecting liposomes that have a liposome size of between about 60 nm to about 1000 nm.

4. The method of claim 1, wherein preparing the liposomes comprises preparing liposomes at size intervals between about 60 to about 1000 nm.

5. The method of claim 1, wherein preparing the liposomes comprises preparing liposomes at size intervals between about 70 nm to about 500 nm.

6. The method of claim 1, wherein said preparing liposomes comprises preparing a solution of lipids.

7. The method of claim 6, wherein the preparing comprises preparing a solution of lipids that comprises a lipid derivatized with a hydrophilic polymer.

8. The method of claim 6, wherein the preparing comprises preparing a solution of lipids effective to form a rigid lipid bilayer.

9. The method of claim 1, further comprising removing from an external liposome suspension medium the condition selected to maintain the compound above its room temperature solubility.

16. A method for preparing liposomes which contain a supersaturated solution of a compound, comprising:

preparing an aqueous supersaturated solution of a compound;

hydrating a lipid film or a lipid solution with said supersaturated solution of the compound to form liposomes;

sizing the liposomes to selected sizes;

analyzing the liposomes at each size for the presence or absence of precipitated compound; and

based on said analyzing, selecting liposomes having a size that corresponds to liposomes having no precipitated compound.